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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/889,874	10/30/2001	James Alun Wynne Morgan	13384-002001	1385

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EXAMINER	
WHITEMAN, BRIAN A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 07/27/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/889,874	MORGAN ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 May 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-53* is/are pending in the application.

4a) Of the above claim(s) *31,34,37,39-42,49,50 and 52* is/are withdrawn from consideration.

5)☒ Claim(s) *32,35, and 51* is/are allowed.

6)☒ Claim(s) *43,45-48 and 53* is/are rejected.

7)☒ Claim(s) *33,36,38,44* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Final Rejection

Claims 31-53 are pending.

The examiner of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be to directed to Brian Whiteman, Art Unit 1635.

Election/Restrictions

Applicant's election with traverse of Group II in the reply filed on 5/19/04 is acknowledged. The traversal is on the ground(s) that both SEQ ID NO: 22 and 23 are encoded by SEQ ID NO: 52. This is not found persuasive for the reasons set forth in the election/restriction mailed on 4/14/04 and because the assertion that sequences existing on the same cosmid (SEQ ID NO: 52) does not support that the sequences share a special technical feature.

The requirement is still deemed proper and is therefore made FINAL.

Claims 31, 34, 37, 39-42, 49, 50, and 52 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 5/19/04.

Claim Objections

Claims 36-43 are objected to because of the following informalities: The status of claims 36-42 is incorrect because of the renumbering of the claims. A marked-up copy of the claims is also missing because of the renumbering of the claims.

The status of Claim 43 is incorrect and a marked-up copy of the claims is missing because the claim was missing from the prior amendment.

Claim 44 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 38. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claims 33, 36 and 53 are objected to because of the following informalities: the claims read on non-elected embodiment.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 43, 45, 46, 47, 48, and 53 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 43, 45, 46, 47, 48, and 53, as best understood, are readable on a genus of isolated nucleic acid sequences, which encodes a polypeptide with at least 70% identity to the polypeptide set forth in SEQ ID NO: 23, wherein the genus of isolated nucleic acid sequences is not claimed in a specific biochemical or molecular structure that could be envisioned by one skilled in the art at the time the invention was made are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification contemplates production of a genus of isolated nucleic molecules that encode a polypeptide with at least 70% identity to the polypeptide set forth in SEQ ID NO: 23 and is a nematode control agent. The specification further contemplates methods of producing the polypeptide. The applicants obtained three strains (C42, I73, H31) using an insect entrapment method. I73 and H31 belong to the species X. bovienii. All three species were determined to have an effective nematocide. I73 was cloned and DNA sequence analysis was performed on the clone. The final sequence of the clone is shown in Figure 2 (37,544 bps) and the corresponding protein sequences are present in Annex 1 (Annex 1 has 51 amino acid sequences). The applicants identified that two regions of the clone were involved in

nematocidial activity, p13-1f (SEQ ID NO: 22) and p14-2f (SEQ ID NO: 23). The as-filed specification provides sufficient description of a species of an isolated nucleic sequence encoding SEQ ID NO: 23. However, there is no evidence of record that p14-2f had a known structural relationship to a genus of nematode control agent DNA sequences. Based upon the prior art and the difference between the nucleotide sequence of SEQ ID NO: 23 and SEQ ID NO: 22 there is expected to be variation among species of DNA sequences that encode nematode control agents. The specification does not describe which nucleotide(s) of the sequence that encodes SEQ ID NO: 23 or what amino acid(s) of SEQ ID NO: 23 are considered essential for the biological activity of a nematode control agent. In view of the above considerations one of skill in the art would not recognize that the specification sufficiently describes a genus of claimed nucleotide sequences because SEQ ID NO: 23 is not a representative species of the claimed genus of isolated nucleotide sequences. It is apparent that on the basis of applicant's disclosure, an adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the invention and reference to potential methods and/or molecular structures of molecules that are essential for the genus of isolated nucleic acid sequences as claimed; what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of biochemical or molecular structures of isolated nucleic acid sequences that must exhibit the disclosed biological functions as contemplated by the claims.

Vas-Cath Inc. v Mhurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purpose of the 'written description' inquiry,

whatever is now claimed." The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath, See MPEP 2163).

With the exception of the nucleic acid sequence encoding SEQ ID NO: 23, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides and/or proteins, regardless of the complexity or the simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. v Chugai Pharmaceutical Co. Ltd., 18 USPQ 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification only provided the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that, "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997): *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement 'by describing the invention, with all it claimed limitations, not that which make it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc. that set forth the claimed invention." *Lockwood*, 107F.3d at 1572, 41 USPQ2d at 1966.
>
> An adequate written description of a DNA, such as the cDNA of the recombinant plasmid and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. *Fiers v. Revel*, 984F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Dir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference

> to a potential method for isolating it; what is required is a description of the DNA itself." Id. At 1170, 25 USPQ at 1606.
>
> The name cDNA is not itself a written description of that DNA; it conveys no distinguishing information, concerning its identity. While the example provides a process for obtaining human insulin-encoding cDNA, there is not further information in the patent pertaining to that cDNA's relevant structural or physical characteristics; in other words, it thus does not describe human insulin cDNA. Describing a method of preparing a cDNA or even describing the protein that the cDNA encodes; as the example does, does not necessarily describe the cDNA itself. No sequence information indication which nucleotides constitute human cDNA appears in the patent, as appears for rat cDNA in Example 5 of the patent. Accordingly, the specification does not provide a written description of the invention of claim 5.

Therefore, only the nucleotide sequence encoding SEQ ID NO: 23, but not the full breadth of the claims (or none of the sequences encompassed by the claim) meets the written description provision of 35 USC 112, first paragraph. The species specifically disclosed is not representative of the genus because the genus of nucleotide sequences encoding a nematode control agent peptide is highly variant.

Applicant's arguments filed 5/28/04 have been fully considered but they are not persuasive.

With respect to applicant's argument that the nucleic acid molecules are defined by their sequence or the sequence of a polypeptide which they encode or by sequence and function (see Eli Lilly 199 F.3d 1563 and The Synopsis of Written Description Guidelines), the argument is not found persuasive because other than teaching that SEQ ID NO: 23 has nematocidial activity, the specification does not disclose which nucleotide(s) of the sequence that encodes SEQ ID NO: 23 or what amino acid(s) of SEQ ID NO: 23 are considered essential for the biological activity of a nematode control agent. In addition, the Examples in the Patent Office's "Synopsis of Application of Written Description Guidelines" are part of training material and are non-binding

and are not cited in the MPEP for determining whether a rejection under 112 first paragraph written description applies to a claimed invention. "The Guidelines do not constitute substantive rulemaking and hence do not have the force and effect of law. They are designed to assist Office personnel in analyzing claimed subject matter for compliance with substantive law. Rejections will be based upon the substantive law, and it is these rejections, which are appealable. Consequently, any perceived failure by Office personnel to follow these Guidelines is neither appealable nor petitionable." See MPEP 2163.

With respect to arguments that the specification provides several working examples of any assay for testing whether a given nucleic acid molecule encodes a polypeptide that is toxic to a nematode (see pages 31-37 of the specification), the argument is not found persuasive because the specification does not provide sufficient description that there is any structure/function relationship between the disclosed polynucleotide sequence encoding SEQ ID NO: 23 and any other sequences that might be embrace by the genus. See MPEP 2163. The assertion that there are assays for testing whether a given nucleic acid molecule encodes a polypeptide that is toxic to a nematode is not found persuasive because the assertion indicates that applicants' were in possession of an assay for testing a given nucleic acid and were not in possession of a genus of nucleic acid molecules encoding a polypeptide that is toxic to nematodes from an assay. Furthermore, in view of the assertion, one skilled in the art would have to make nucleic acid molecules and use the assays for testing whether or not a given nucleic acid molecule encodes a polypeptide that is toxic to a nematode. Thus, the assertion indicates that at the time of filing applicants were not in possession of the claimed genus of isolated nucleotide sequences.

Claims 43, 45, 46, 47, 48, and 53 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated nucleotide sequence encoding the polypeptide set forth in SEQ ID NO: 23, does not reasonably provide enablement for an isolated nucleotide sequence encoding a polypeptide with up to 98% identity to SEQ ID NO: 23. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The invention lies in the field of producing a genus of isolated nucleic acid molecules encoding a polypeptide with at least 70% identity to the polypeptide sequence set forth in SEQ ID NO: 23 and using the isolated nucleic acid molecule for generating a toxic response in a nematode.

The as-filed specification does not provide sufficient guidance and/or factual evidence for one skilled in the art to make and/or use a sequence having at least 70% identity to the sequence presented as SEQ ID NO: 23 other than the sequence itself. The claims embrace a polynucleotide that encodes a polypeptide and wherein the sequences is at least 70% sequence identity to the sequence presented in SEQ ID NO: 23. The claimed invention embraces polynucleotide sequence encoding a polypeptide with or without nematocidial activity. The specification fails to provide guidance as to which (if any) of the amino acids may be changed while activity is retained. There are 1,673 amino acids in the polypeptide sequence set forth in SEQ ID NO: 23. The total number of 1,673 amino acid peptides is 4×10^{2176}. The number of single amino acid substitutions is 33,460. The number of two amino acid substitutions is over 5×10^{8}. The teaching in the specification do not commensurate in scope with the claims because the breadth of the claims embrace a large number of possible sequences that differ from SEQ ID

NO: 23 by substitution of up to 30% of its amino acids, which would be a substitution of up to 501 amino acids of SEQ ID NO: 23. To determine the number of possible amino acid sequences, N, with 501 substitutions, one skilled in the art would use the formula [(N=x^nL!/n!(L-n)!), where x=19 (number of possible amino acids that could replace an amino acid at any one position in SEQ ID NO: 23), L=1673 (amino acid length of SEQ ID NO: 23), n=501,] or $3x10^{1082}$ possible sequences. This is a lower limit of the number of possible sequences because the claims also embrace insertions or deletions of amino acids in SEQ ID NO: 23 that the equation does not take into account. It is known for nucleic acids as well as proteins, for example, that even a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many instances, albeit not in all cases. The specification does not provide sufficient guidance and/or factual evidence that it was routine to substitute or delete at least two nucleotides of a nucleotide sequence and determine which nucleotide sequences meet the functional limitation of the claims. The effects of these changes is largely unpredictable as to which ones have a significant effect versus not. Several publications document this unpredictability of the relationship between sequence and function, albeit that certain specific sequences may be found to be conserved over polypeptides of related function upon a significant amount of further research. See the following publications that support this unpredictability as well as noting certain conserved sequences in limited specific cases: Baker et al., Science, 294:pages 93-96, 2001); Attwood, T (*Science*, vol. 290, no. 5491, pp. 471-473, 2000); Gerhold et al., (*BioEssays*, vol. 18, no. 12, pp. 973-981, 1996); Russell et al., *Journal of Molecular Biology*, vol. 244, pp 332-350, 1994); and Wells et al., *Journal of Leukocyte Biology*, vol. 61, no. 5, pp. 545-550, 1997). Because of this lack of guidance, the extended experimentation that would be

required to determine which substitutions would be acceptable to retain activity, and the fact that the relationship of the sequence of a peptide and its tertiary structure (*e.g.* its activity) are not well understood and are not predictable (Ngo et al. The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495), it would require an undue amount of experimentation for one skilled in the art in view of the prior art to arrive at other sequences that have at least 70% sequence identity to a polypeptide encoded by SEQ ID NO: 23 and still possess nematocidial activity. Since it would require undue experimentation to identify other polypeptides that have nematocidial activity, it certainly would require undue experimentation to make their corresponding DNA, and therefore, the entire scope of the claimed invention.

In conclusion, the as-filed specification and claims coupled with the art of record, at the time the invention was made, only provide sufficient guidance and/or evidence to reasonably enable making and using an isolated nucleotide sequence encoding the polypeptide set forth in SEQ ID NO: 23, does not reasonably provide enablement for a genus of polynucleotide sequences encoding a polypeptide having at least 70% sequence identity to the sequence presented in SEQ ID NO: 23. One skilled in the art would have to engage in a large quantity of experimentation in order to practice the claimed invention based on the In Re Wands Factors including the lack of guidance in the application's disclosure, the unpredictability of producing nucleotide sequences encoding a polypeptide with at least 70% identity to SEQ ID NO: 23.

Applicant's arguments filed 5/28/04 have been fully considered but they are not persuasive.

With respect to applicants argument that given the teachings in the specification, one skilled in the art could make and use the nucleic acids without undue experimentation because the specification teaches one skilled in the art how to identify nucleic acid molecules encoding biologically active polypeptides, the argument is not found persuasive because the specification must be enabling at the time the application was filed not after the application the filed. See MPEP 2164.05(a). The specification fails to provide sufficient guidance and/or factual evidence that it was routine for one skilled in the art to screen at least 3×10^{1082} amino acid peptide for peptides that meet or do not meet the limitations set forth in the claims.

With respect to applicants' argument that it is clear the relative skill in the art of generating variant polypeptides is very high and those skilled in the art are aware of various random mutagenesis protocols that can be used to create libraries of clones encoding variant polypeptides, the argument is not found persuasive because the applicants do not provide any factual evidence to support their assertion(s). See MPEP 608.01(p). Furthermore, the rejection is not directed to whether or not one skill in the art can produce clones encoding variant polypeptides, the main point of the rejection is that in view of the lack of guidance provided by the specification for making and using the claimed genus of isolated nucleic acid molecules, it would take one skilled in the art an undue amount of experimentation to make and screen at least 3×10^{1082} amino acid peptide for polypeptides that meet or do not meet the limitations set forth in the claims.

With respect to applicants position that the claims are not excessively broad encompassing as they do nucleic acid molecules encoding polypeptides having at least 70%,

85%, 90%, 95%, or 98% to a reference polypeptide (SEQ ID NO: 23), the argument is not found persuasive because the breadth of the claims encompasses at least 3×10^{1082} amino acid peptide.

With respect to applicants argument that with respect to predictability, although it cannot always be predicted whether a given amino acid change will alter function, it is generally understood, despite some exceptions, that certain variants, e.g., those involving conservative amino acid substitutions are more likely to retain function, the argument is not found persuasive because the claims embrace both conservative and non-conservative amino acid substitutions. The prior art is absent that is was routine for one skilled in the art to substitute several amino acids (e.g., 200 amino acids) in a polypeptide and determine if the polypeptide retains a desired biological property. See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Furthermore, the as-filed specification and the prior art do not provide evidence that is was routine for one skilled in the art to use random mutagenesis protocols to produce a library of polypeptides and then use a high-throughput screening method to screen at least 3×10^{1082} amino acid peptide for polypeptides that meet or do not meet the limitations set forth in the claims.

Conclusion

Claims 32, 35, and 51 are in condition for allowance because the claims are free of the prior art of record.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (571) 272-0764. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, SPE - Art Unit 1635, can be reached at (571) 272-0760.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

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